DOI:10.11817/j.issn.1672-7347.2018.04.014
www.csumed.org/xbwk/fileup/PDF/201804421.pdf

Leukocyte miR-223-3p is not associated with altered platelet responses to clopidogrel in patients with coronary artery disease

XIE Wenjian[1], YIN Qian[2], ZHANG Mengran[2], LI Shengnan[3], CHEN Shaoliang[1]

(1. Department of Cardiology, Affiliated Nanjing Hospital of Nanjing Medical University, Nanjing 210006;
2. General Clinical Research Center, Affiliated Nanjing Hospital of Nanjing Medical University, Nanjing 210006;
3. Department of Pharmacology, School of Basic Medical Sciences, Nanjing Medical University, Nanjing 211166, China)

ABSTRACT

Objective: To investigate the potential correlation between miR-223 level in leukocytes and platelet responses to clopidogrel in patients with coronary artery disease.

Methods: A cohort of 188 outpatients, who conducted percutaneous coronary intervention (PCI) and received dual antiplatelet therapy, were recruited. The patient's electronic health data were collected, and their blood samples were obtained for measurement of adenosine diphosphate (ADP)-induced whole-blood platelet aggregation. Extreme cases of platelet responses to clopidogrel (ultra- vs. non-responder) were measured with miR-223-3p levels in leukocytes.

Results: Both groups had similar miR-223-3p levels in leukocytes. There were no significant differences in other demographic and clinical data except for metrics of ADP-induced whole-blood platelet aggregation between the 2 group.

Conclusion: MiR-223-3p in peripheral leukocytes is not associated with the altered platelet responses to clopidogrel in PCI outpatients.

KEY WORDS clopidogrel; platelet; coronary artery disease; miR-223

冠心病患者白细胞miR-223-3p水平与氯吡格雷治疗后的血小板反应无关

谢文剑[1]，殷蒨[2]，张梦然[2]，李胜男[3]，陈绍良[1]

Date of reception: 2017-04-28

First author: XIE Wenjian, Email: jimxwj@126.com

Corresponding author: LI Shengnan, Email: snli@njmu.edu.cn; CHEN Shaoliang, Email: chemngx@126.com

Foundation item: This work was supported by the National Natural Science Foundation (81473286) and Clinical Medicine Science and Technology Projects of Jiangsu Province (BL2013001), China.

(南京医科大学 1. 附属南京医院心内科，南京 210006；2. 附属南京医院临床研究中心，南京 210006；
3. 基础医学院药理学系，南京 211166)

[摘要] 目的：探讨冠心病患者白细胞miR-223-3p水平与氯吡格雷治疗后血小板反应之间的潜在相关性。**方法：**收集188名择期经皮冠状动脉介入治疗(percutaneous coronary intervention，PCI)术后接受双重抗血小板治疗的门诊患者的一般资料和血标本，检测二磷酸腺苷(adenosine diphosphate，ADP)诱导的全血血小板聚集率。选取血小板反应有显著差异的患者(超反应组和无反应组)，检测其白细胞miR-223-3p水平。**结果：**除ADP诱导的全血血小板聚集率外，两组患者的一般资料和白细胞miR-223-3p水平差异无统计学意义(P>0.05)。**结论：**冠心病择期PCI术后门诊患者外周血白细胞miR-223-3p水平与氯吡格雷治疗后的血小板反应无关。

[关键词] 氯吡格雷；血小板；冠心病；miR-223

In clinical settings, not all patients would respond well to clopidogrel due to pronounced inter-individual differences in their genetic make-up, which results in differential exposure to or response to clopidogrel active metabolite (CAM) in patient care[1-2]. However, the factors known to lead to that variability just account for less than 20% of the overall variation in platelet responses to clopidogrel[3], suggesting that other unknown factors may be involved in such variability as well.

As one of the epigenetic factors, small non-coding RNA (also known as microRNA, miRNA, or miR) species, defined as a class of endogenous, 21- to 24-nucleotide long RNA molecules, can regulate mRNA translation through binding to complementary regions of certain mRNA to repress mRNA translation or to induce mRNA degradation[4–7]. In human mature (or anucleate) platelets, there is an miRNA pathway[4, 8], where platelet-derived miRNAs may function as biomarkers that reflect inter-individual variability in the susceptibility to cardiovascular diseases and platelet-derived miRNAs may respond to intervention[4-5, 9]. Of them, miR-223 is such a well-characterized small RNA molecule[10]. An earlier clinical study[11] indicated that decreased platelet miR-223 expression is associated with high on-clopidogrel platelet reactivity in non-diabetic patients with non-ST elevation (NSTE) acute coronary syndrome (ACS) who had been scheduled for percutaneous coronary intervention (PCI). Subsequently, an extended observation[12] demonstrated that decreased plasma miR-223 levels can be used to predict high on-clopidogrel platelet reactivity in patients with troponin-negative NSTE-ACS. Moreover, another independent clinical investigation[13] suggested that elevated plasma miR-223 levels are associated with enhanced platelet responsiveness to dual antiplatelet therapy. These studies[11–13] argue against the notion of low plasma miR-223 level as a surrogate biomarker of efficacy of platelet inhibition in healthy subjects treated with prasugrel alone or in combination with aspirin[9]. However, some evidence did not support that plasma miR-223 level is an independent predictive biomarker for major adverse cardiovascular events in PCI patients treated with dual antiplatelet therapy[14]. Small sample size and marked heterogeneity across subjects enrolled, and platelet function test used may lead to inconsistent results across clinical research studies[9, 11–13, 15]. Therefore, the effects of miR-223 on on-clopidogrel platelet reactivity should be replicated and validated further.

In humans, miR-223 from leukocytes and platelets is the most abundant cell-free miRNA in blood[16]. Activated platelets would aggregate with circulating leukocytes (e.g. monocytes and neutrophils) and form circulating leukocyte-platelet aggregates (LPAs), and elevated circulating LPAs (monocyte LPAs in particular) are linked to atherothrombosis in high-risk patients[17-18]. On the other hand, clinical studies observed that clopidogrel can reduce the formation of monocyte LPAs[19–21], and that antiplatelet therapy can decrease plasma miR-223 levels [9]. However, little is known about the effects of miR-223 in peripheral leukocytes on the responses to clopidogrel in patients with coronary artery disease. In this study, we recruited outpatients who had undergone PCI to determine whether or not there are statistically significant differences in miR-223 levels in leukocytes between the ultra-responder (UR) and non-responder (NR) to clopidogrel as identified by ADP-induced platelet aggregation ex vivo.

1 Subjects and methods

1.1 Patients selection

A total of 188 outpatients with NSTE-ACS were recruited from the Division of Cardiology, Department

of Medicine, Nanjing First Hospital, Nanjing Medical University, China. The diagnosis of NSTE-ACS was based on published Diagnostic Criteria for Coronary Atherosclerotic Heart Disease in 2010[22]. All patients received clopidogrel (75 mg/d) and aspirin (100 mg/d) for more than 6 months after elective PCI. Exclusion criteria were as follows: Allergic reactions or contraindications to clopidogrel; use of the thienopyridine, glycoprotein IIb/IIIa inhibitor, and warfarin before recruitment; coronary artery bypass graft; stent thrombosis; severe blood disease (e.g. purpura haemorrhagica); high bleeding risk; chronic liver or kidney failure [estimated glomerular filtration rate <30 mL/(min·1.73 m^{-2})]; malignant tumor; life expectancy of less than one year; blood platelet count <125×10^9/L or >350×10^9/L; and pregnant women. The study protocol was approved by the Ethics Review Committee of Nanjing First Hospital, Nanjing Medical University, China, and written informed consent was received from each patient.

1.2 Inhibition of ADP-induced platelet aggregation by clopidogrel

Venous blood samples were obtained from each patient 1–2 h after taking maintenance dose of 75 mg clopidogrel and were withdrawn into sodium citrate-containing tubes. Measurement of ADP-induced whole-blood platelet aggregation was described elsewhere[23-24]. In brief, 0.5-mL whole blood was diluted with equal volume of 0.9% saline solution and pre-warmed at 37 ℃ for 10 min. Platelet aggregation was measured by a whole-blood aggregometer (Chrono-log model 590-2D, US) at 1 min after adding 10 μmol/L ADP. Platelet aggregation was measured as a value of electronic impedance (Ω) between the two electrodes immersed in a diluted sample, which reflects direct adhesion of activated platelets to the surface of metal electrodes and subsequent formation and accumulation of aggregated platelets[25–28]. Changes in impedance were recorded for 3 min, and the impedance values were used for the analysis. For patients treated with clopidogrel, a value of electronic impedance of >10 Ω[27–29] was defined as NR to clopidogrel, whereas a value of equal to or less than 1 Ω was defined as UR.

1.3 Measurement of miR-223-3p by quantitative real-time PCR

Total RNA was extracted from isolated peripheral blood leukocytes of NR and UR patients using TRIzol reagent (Life Technologies, US) according to the manufacturer's protocol. Total RNA was purified using miRNeasy Mini Kit (50) (QIAGEN, Germany) and checked for a RNA Integrity Number (RIN) to inspect RNA integration by an Agilent Bioanalyzer 2100 (Agilent technologies, US). Samples with RIN<6 and 28S/18S<0.7 were excluded. Qualified total RNA was subjected to the synthesis of the first cDNA strand in a total volume of 25 μL with looped reverse-transcription (RT) primers and Taqman MicroRNA Reverse Transcription Kit (ABI, US). Primer sequences for hsa-miR-223-3p and internal reference U6 were as follows: hsa-miR-223-3p, 5'-UGUCAGUUUGUCAAAUACCCCA-3'; and U6, 5'-GTGCTCGCTTCGGCAGCACATATACTAAAATTG-GAACGATACAGAGAAGATTAGCATGGCCCCTGC-GCAAGGATGACACGCAAATTCGTGAAGCGTTCC-ATATTTT-3'.

The RT reactions were conducted at 16 ℃ for 30 min, 42 ℃ for 30 min, 85 ℃ for 5 min, and finally 4 ℃ for cooling. Subsequently, Taqman quantitative real-time PCR was conducted with Taqman Universal PCR Master Mix (ABI, US). The real-time PCR amplification was conducted in a total volume of 10 μL with template cDNA, Taqman MicroRNA Assay Mix, Taqman Universal PCR buffer, and sterilized water. Cycling profile was 50 ℃ for 2 min, 95 ℃ for 10 min, followed by 40 cycles of 95 ℃ for 15 s and 60 ℃ for 1 min. Amplification and quantification were performed with ABI 7 900 HT Sequence Detection System (ABI, US). All samples were run in triplicates by a biotech company (Shanghai Biotechnology Co., China). Hsa-miR-223-3p expression was quantified using the comparative threshold cycle (Ct) method ($2^{-\Delta\Delta Ct}$) relative to U6 (an endogenous control).

1.4 Statistical analysis

Analysis of clinical variables was performed using SPSS 20.0 software (SPSS Inc., US). Continuous variables are presented as mean and standard deviation ($\bar{x}\pm s$) and were compared using Student's *t*-test. Categorical variables are presented as absolute number and percentage, and were compared by Chi-square or Fisher's exact test, as appropriate. A $P<0.05$ was considered statistically significant.

2 Results

Clinical phenotypes of interest—NR or UR to

clopidogrel—were identified by ADP-induced platelet aggregation as measured with electronic impedance values (Figure 1). Clinical characteristics and clopidogrel responses between NR and UR groups are summarized in Table 1. The impedance values ranged from 0 to 1 Ω in the UR group and from 12 to 21 Ω in the NR group. UR exhibited significantly lower ADP-induced platelet aggregation than NR (0.7±0.5 vs. 15.0±2.5, P<0.001). However, there were similar distributions in other clinical characteristics between the 2 groups, such as age, gender, BMI, smoking, bleeding events, previous PCI or stroke, diabetes mellitus, dyslipidemia, hypertension, and concomitant use of other select medications, except for more use of beta blockers in the NR group.

A total of 24 RNA samples in the UR group and 36 RNA samples in the NR group were used for the quantification of leukocyte hsa-miR-223-3p by quantitative real-time PCR. As shown in Figure 2, there was no statistically significant difference in hsa-miR-223-3p levels in leukocytes between the NR and UR groups. Moreover, there was no significant correlation between hsa-miR-223-3p levels in leukocytes and ADP-induced platelet aggregation as shown in Figure 3.

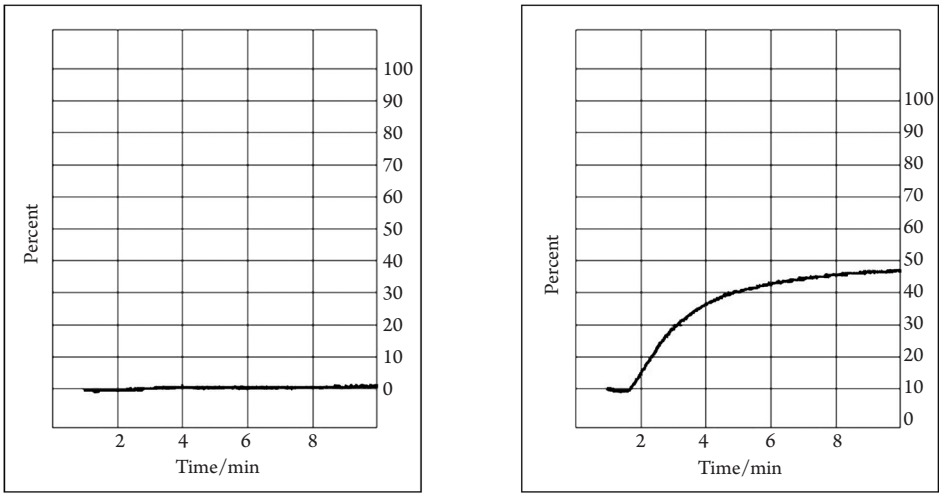

Figure 1 Representative tracing of ADP-induced platelet aggregation in an ultra-responder (left) vs a non-responder (right)

Table 1 Demographic data and clinical profile of the recruited patients

Groups	n	Platelet aggregation/Ω	Age/year	Male/[No.(%)]	BMI/(kg·m^{-2})	Bleeding/[No.(%)]	Previous PCI/[No.(%)]
UR	24	0.7±0.5	61.7±11.3	18(75)	25.5±3.9	1(4)	1(4)
NR	36	15.0±2.5	65.9±11.3	23(64)	24.8±2.8	0(0)	2(6)
P		<0.001	0.158	0.373	0.427	0.328	0.813

Groups	Previous stroke/[No.(%)]	Smoker/[No.(%)]	Hypertension/[No.(%)]	Diabetes/[No.(%)]	Dyslipidemia/[No.(%)]	Use of ACEI/[No.(%)]
UR	1(4)	11(46)	14(58)	6(25)	16(67)	3(13)
NR	6(17)	17(47)	26(72)	10(28)	28(78)	4(11)
P	0.918	0.918	0.271	0.815	0.349	0.872

Groups	Use of beta blocker/[No.(%)]	Use of CCA/[No.(%)]	Use of diuretics/[No.(%)]	Use of ARB/[No.(%)]	Use of statin/[No.(%)]
UR	2(8)	9(38)	1(4)	4(17)	5(21)
NR	11(31)	16(44)	1(3)	5(14)	3(8)
P	0.032	0.600	0.774	0.842	0.204

Data of platelet aggregation, age, and BMI are presented as $\bar{x}\pm s$. BMI: Body mass index; PCI: Percutaneous coronary intervention; ACEI: Angiotensin-converting enzyme inhibitor; CCA: Calcium channel antagonist; ARB: Angiotensin receptor blocker

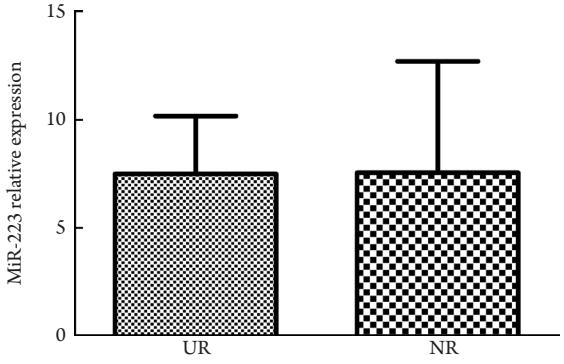

Figure 2 Differences in miR-223-3p levels in leukocytes between ultra-responders (*n*=24) and non-responders (*n*=36) to clopidogrel

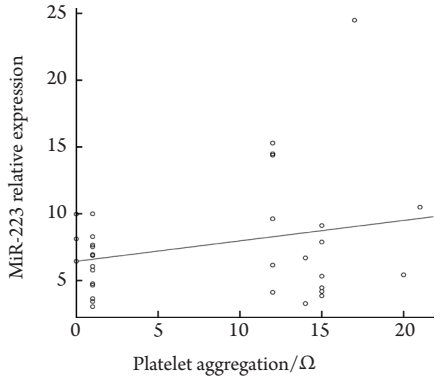

Figure 3 Correlation between miR-223-3p expression levels in leukocytes and ADP-induced whole-blood platelet aggregation

3 Discussion

In this study, we observed that miR-223-3p levels in peripheral leukocytes did not differ significantly between ultra- and non-responders to clopidogrel, suggesting that leukocyte-derived miR-223 might not be involved in altered platelet response to clopidogrel, inconsistent with the conclusions made by previous studies[11-13].

Some earlier clinical studies[12-13] found that decreased miR-223 levels in plasma is associated with high on-clopidogrel platelet reactivity (i.e., blunted platelet responses to clopidogrel), which argues against the notion that the plasma miR-223 level is not an independent predictive marker for major adverse cardiovascular events after dual antiplatelet therapy in patient care[14]. Although the sample size of patients in this study was not large enough, the use of the extreme cases of platelet responses to clopidogrel (UR vs NR) for further datum analysis would make this study more sensitive to reflect a potential association of miR-223 with altered platelet responses to clopidogrel compared with other similar clinical studies[11–13]. This is because paired extreme phenotype cases from the 2 ends of the population distribution exhibit the opposite phenotypes (UR vs NR), with no any overlapping present between them[30]. Through such highly sensitive approach (extreme-case groups)[30], our preliminary clinical observation indicates that platelet responsiveness to clopidogrel may not vary by the expression level of miR-223 in peripheral leukocytes. In contrast, patients were grouped by dichotomization or tertile with marked overlapping in between[11-13]. In addition, the cellular sources of miR-223 are different between previous studies[11-13] and ours. The potential causes could be used to explain the inconsistence of all results.

The miRNA-deficient mouse model can be used to reveal the role of a certain miRNA of interest in the physiological and pathophysiological processes involved. In miR-223-null mice[31], absence of miR-223 did not affect platelet nature, including platelet number, volume, and lifespan, expression levels of platelet surface receptors, platelet adhesion and activation, and in particular, ADP-induced, adhesion, and aggregation, indicating no marked alterations in platelet activation in miR-223-absent mice. Furthermore, there are no marked changes in both the spleen (which sequesters platelets) and megakaryocytes (which produce platelets in bone marrow)[31]. The above evidence strongly suggests that platelet functions are not dependent upon the presence and expression of miR-223[32]. According to the conclusions drawn from miR-223-deficient mouse model[31], it is not surprising that miR-223 in leukocytes is not involved in altered platelet responses to clopidogrel.

There were some limitations to this study. Firstly, in the UR group (*n*=47) and the NR group (*n*=47), only 24 and 36 samples were analyzed, respectively, due to RNA quality issue (some samples were stored over 6 month), indicating that 30% of the entire samples were excluded. Secondly, the use of beta blockers in the NR group was more than that in the UR group. Some beta blockers had antiplatelet aggregation effect and reduced electric resistance. Thirdly, this study did not measure miR-

223 levels in plasma and platelet. Lastly, no subtype of leukocytes was analyzed.

In summary, miR-223-3p levels in leukocytes are not significantly different between UR and NR to clopidogrel in elective PCI patients treated with dual antiplatelet therapy for more than 6 months, suggesting that miR-223 in peripheral leukocytes may not be a useful biomarker for reflecting platelet responses to clopidogrel in patient care.

Acknowledgments

The measurement of ADP-induced platelet aggregation was performed in the Laboratory of Professor XIE Hongguang, General Clinical Research Center, Nanjing Hospital Affiliated to Nanjing Medical University, China. And part of this work was also supported by Professor XIE.

References

[1] Xie HG, Zou JJ, Hu ZY, et al. Individual variability in the disposition of and response to clopidogrel: Pharmacogenomics and beyond[J]. Pharmacol Ther, 2011, 129(3): 267-289.

[2] Siasos G, Stefanadis C, Tousoulis D. Factors affecting platelet reactivity and cardiovascular outcome in CAD patients treated with P2Y12 receptor inhibitors[J]. J Am Coll Cardiol, 2016, 68(1): 134.

[3] Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy[J]. JAMA, 2009, 302(8): 849-857.

[4] McManus DD, Freedman JE. MicroRNAs in platelet function and cardiovascular disease[J]. Nat Rev Cardiol, 2015, 12(12): 711-717.

[5] Engelhardt S. Small RNA biomarkers come of age[J]. J Am Coll Cardiol, 2012, 60(4): 300-303.

[6] Bartel DP. MicroRNAs: Target recognition and regulatory functions [J]. Cell, 2009, 136(2): 215-233.

[7] Guo H, Ingolia NT, Weissman JS, et al. Mammalian microRNAs predominantly act to decrease target mRNA levels[J]. Nature, 2010, 466(7308): 835-840.

[8] Landry P, Plante I, Ouellet DL, et al. Existence of a microRNA pathway in anucleate platelets[J]. Nat Struct Mol Biol, 2009, 16(9): 961-966.

[9] Willeit P, Zampetaki A, Dudek K, et al. Circulating microRNAs as novel biomarkers for platelet activation[J]. Circ Res, 2013, 112(4): 595-600.

[10] Shi R, Zhou X, Ji WJ, et al. The emerging role of miR-223 in platelet reactivity: Implications in antiplatelet therapy[J]. Bio Med Res Int, 2015, 2015: 981841.

[11] Shi R, Ge L, Zhou X, et al. Decreased platelet miR-223 expression is associated with high on-clopidogrel platelet reactivity[J]. Thromb Res, 2013, 131(6): 508-513.

[12] Zhang YY, Zhou X, Ji WJ, et al. Decreased circulating microRNA-223 level predicts high on-treatment platelet reactivity in patients with troponin-negative non-ST elevation acute coronary syndrome[J]. J Thromb Thrombolysis, 2014, 38(1): 65-72.

[13] Chyrchel B, Toton-Zuranska J, Kruszelnicka O, et al. Association of plasma miR-223 and platelet reactivity in patients with coronary artery disease on dual antiplatelet therapy: A preliminary report[J]. Platelet, 2015, 26(6): 593-597.

[14] Yu XY, Chen JY, Zheng ZW, et al. Plasma miR-126 as a potential marker predicting major adverse cardiac events in dual antiplatelet-treated patients after percutaneous coronary intervention[J]. EuroIntervention, 2013, 9(5): 546-554.

[15] Cattaneo M. Variability of platelet responses to adenosine diphosphate[J]. Thromb Res, 2013, 131(6): 472-473.

[16] Shan Z, Qin S, Li W, et al. An endocrine genetic signal between blood cells and vascular smooth muscle cells: Role of microRNA-223 in smooth muscle function and atherogenesis[J]. J Am Coll Cardiol, 2015, 65(23): 2526-2537.

[17] Cerletti C, Tamburrelli C, Izzi B, et al. Platelet-leukocyte interactions in thrombosis[J]. Thromb Res, 2012, 129(3): 263-266.

[18] Nagasawa A, Matsuno K, Tamura S, et al. The basis examination of leukocyte-platelet aggregates with CD45 gating as a novel platelet activation marker[J]. Int J Lab Hematol, 2013, 35(5): 534-541.

[19] Gremmel T, Eslam RB, Koppensteiner R, et al. Prasugrel reduces agonists' inducible platelet activation and leukocyte-platelet interaction more efficiently than clopidogrel[J]. Cardiovasc Ther, 2013, 31(5): e40-e45.

[20] Braun OO, Johnell M, Varenhorst C, et al. Greater reduction of platelet activation markers and platelet-monocyte aggregates by prasugrel compared to clopidogrel in stable coronary artery disease[J]. Thromb Haemost, 2008, 100(4): 626-633.

[21] Hosokawa K, Ohnishi T, Sameshima H, et al. Analysing responses to aspirin and clopidogrel by measuring platelet thrombus formation under arterial flow conditions[J]. Thromb Haemost, 2013, 109(1): 102-111.

[22] 中华人民共和国卫生部.冠状动脉粥样硬化性心脏病诊断标准[S].北京：中国标准出版社, 2010: 1-14.
Ministry of Public Health of the People's Republic of China. Diagnostic criteria for coronary atherosclerotic heart disease[S]. Beijing: China Standards Press, 2010: 1-14.

[23] Yin Q, Tai T, Ji JZ, et al. Interleukin-10 does not modulate clopidogrel platelet response in mice[J]. J Thromb Haemost, 2016, 14(3): 596-

605.

[24] Tai T, Mi QY, Ji JZ, et al. Enhanced platelet response to clopidogrel in Abcc3-deficient mice due to its increased bioactivation[J]. J Cardiovasc Pharmacol, 2016, 68(6): 433-440.

[25] Cardinal DC, Flower RJ. The electronic aggregometer: A novel device for assessing platelet behavior in blood[J]. J Pharmacol Methods, 1980, 3(2):135-158.

[26] Femia EA, Scavone M, Lecchi A, et al. Effect of platelet count on platelet aggregation measured with impedance aggregometry (multiplate analyzer) and with light transmission aggregometry[J]. J Thromb Haemost, 2013, 11(12): 2193-2196.

[27] Neubauer H, Kaiser AF, Endres HG, et al. Tailored antiplatelet therapy can overcome clopidogrel and aspirin resistance—the BOchum CLopidogrel and Aspirin Plan (BOCLA-Plan) to improve antiplatelet therapy[J]. BMC Med, 2011, 9: 3.

[28] 乔蕊, 王京, 李蕾, 等. 全血电阻法检测血小板聚集程度对抗血小板治疗效果的评价[J]. 中华检验医学杂志, 2007, 30(11): 1260-1265.
QIAO Rui, WANG Jing, LI Lei, et al. Quantifying the effect of antiplatelet therapy by whole blood platelet aggregometry[J]. Chinese Journal of Laboratory Medicine, 2007, 30(11): 1260-1265.

[29] 李蕾, 韩江莉, 李海燕, 等. 冠心病患者氯吡格雷抵抗与血小板参数的相关性分析[J]. 中华医学杂志, 2013, 93(12): 916-920.
LI Lei, HAN Jiangli, LI Haiyan, et al. Clopidogrel resistance of patients with coronary artery disease and its correlation with platelet count and mean platelet volume[J]. National Medical Journal of China, 2013, 93(12): 916-920.

[30] Scott SA, Collet JP, Baber U, et al. Exome sequencing of extreme clopidogrel response phenotypes identifies B4GALT2 as a determinant of on-treatment platelet reactivity[J]. Clin Pharmacol Ther, 2016, 100(3): 287-294.

[31] Leierseder S, Petzold T, Zhang L, et al. miR-223 is dispensable for platelet production and function in mice[J]. Thromb Haemost, 2013, 110(6): 1207-1214.

[32] Halkein J, de Windt LJ. miR-223: Sailing to terra incognita for microRNAs in platelets[J]. Thromb Haemost, 2013, 110(6): 1112-1113.

(Edited by CHEN Liwen)

本文引用： 谢文剑, 殷蒨, 张梦然, 李胜男, 陈绍良. 冠心病患者白细胞miR-223-3p水平与氯吡格雷治疗后的血小板反应无关[J]. 中南大学学报(医学版), 2018, 43(4): 421-427. DOI:10.11817/j.issn.1672-7347.2018.04.014

Cite this article as: XIE Wenjian, YIN Qian, ZHANG Mengran, LI Shengnan, CHEN Shaoliang. Leukocyte miR-223-3p is not associated with altered platelet responses to clopidogrel in patients with coronary artery disease[J]. Journal of Central South University. Medical Science, 2018, 43(4): 421-427. DOI:10.11817/j.issn.1672-7347.2018.04.014